REMARKS

Upon entry of the foregoing amendments, claims 2, 26-32, 34, 39, and 43-50 are pending in the present application. Claims 24 and 25 have been canceled without prejudice. Claims 2, 30, 32, and 34 have been amended, and claims 43-50 have been added. Support for the amendments and new claims can be found throughout the original claims and specification (e.g., page 2, lines 3-14, original claim 33, and the paragraph bridging pages 16 and 17). No new matter has been added.

Claims 2 and 24-42 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ruff et al. in view of Longenecker et al. and Byun et al.

As previously made of record, although Ruff et al. describe coupling a peptide to a bile acid to make similar compounds, Ruff et al. merely teach use of those compounds for attaining analgesia and administration of those compounds by subcutaneous injection (see, column 2, lines 29 and 38). In contrast, the present claims as amended are directed to methods and compositions for administering a peptide conjugate orally. Ruff et al. neither teach nor suggest oral administration of the compounds and compositions disclosed therein. In particular, Ruff et al. neither teach nor suggest a pharmaceutical composition that is coated for oral administration as recited in amended claim 39.

Applicants point out that one of ordinary skill in the art would not be motivated to adapt the teachings of Ruff et al. (i.e., administration by subcutaneous injection) to oral administration because an orally administrated peptide conjugate would be expected to degrade in the stomach and fail to pass into the gut. For this reason, one of ordinary skill in the art would not have been motivated to apply the teachings of Ruff et al. to oral administration, and could have had no reasonable expectation of success for surmounting this obstacle. In contrast, the present specification teaches that a peptide conjugate as set forth in Formula II can be effectively administered orally, despite the harsh environment of the digestive tract.

Moreover, Ruff et al. provide no motivation for one skilled in the art to make the pharmaceutical composition that is coated as recited in claim 39, because Ruff et al. teach administration of compounds only by subcutaneous injection, and such a coating would be unsuitable in that context.

The other references cited in the Office Action fail to overcome the deficiencies of Ruff et al. As the Office Action concedes, Longenecker et al. carries little weight; it is cited merely for the teaching of insulin as a therapeutic peptide in the general context of bile acids. Nothing in this reference would lead one of ordinary skill in the art to conjugates of bile acids and insulin or any other polypeptides, nor is there any evidence that would overcome the doubts of one of ordinary skill in the art as discussed above.

While Byun et al. disclose bile acid conjugates for oral administration, their conjugates are polysaccharide conjugates, not polypeptide conjugates as presently being claimed. Accordingly, Byun et al., taken alone or with the other references, fails to provide a reasonable expectation of success, since one of ordinary skill in the art could not expect that polypeptide conjugates would survive degradation in the digestive tract and retain their activity following oral administration. Moreover, as Applicants previously argued and as the Office Action admits, Swaan et al. (a reference dated *later* than Ruff et al.) specifically teach that peptides of 6 amino acid residues in length were not actively absorbed. Thus, one of ordinary skill in the art would be dissuaded from using bile acids conjugated to peptides of 6 or more amino acids in length for orally administered treatments. The teachings of Ruff et al., which relate only to administration by injection, fail to counterbalance the weight of the negative teachings of Swaan et al.

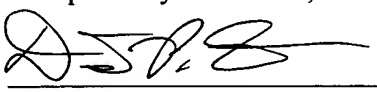
In addition, Ruff et al. disclose a further negative teaching that detracts from the motivation of one of ordinary skill in the art to arrive at the presently claimed invention, or to have any reasonable expectation of success in doing so: In column 3, lines 5-8, Ruff et al. point out that their conjugate does not enhance uptake of calcium content into bones. Thus, Ruff et al. admit that the primary hormonal activity of calcitonin is lost in the context of their invention. This revelation further fuels the doubts of one of ordinary skill in the art, and is particularly compelling with respect to the present claims as amended, as insulin, calcitonin, secretin, and gastrin are effective in the treatment of the conditions recited in the pending claims due to their hormonal activities.

The conclusion that the cited references, taken singly or together, teach away from the presently claimed invention is inescapable. At the very least, Applicants submit that the pending claims as amended are nonobvious because the cited prior art references, taken alone or in combination, fail to establish a *prima facie* case of obviousness.

For the above reasons, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited.

Although Applicants believe no fees are due with this submission, the Commissioner is hereby authorized to credit any overpayment or charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Respectfully Submitted,



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